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A LÆVO-ROTATORY MODIFICATION

OF

QUERCITOL

BY

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AND

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COLLEGE OF SURGEONS OF ENGLAND
JUL

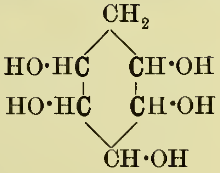
LXII.—*A Lævorotatory Modification of Quercitol.*

By Frederick Belding Power and Frank Tutin.

Quercitol has hitherto only been found in the fruits (acorns) of certain species of *Quercus*, in which it exists as a dextrorotatory modification. The lævorotatory modification now described was obtained by us from the leaves of *Gymnema sylvestre* (Br.), a plant belonging to the family of *Asclepiadaceæ*, and indigenous to Banda and the Deccan Peninsula (compare "Pharmacographia Indica," vol. II, p. 450).

In the course of an examination of a large quantity of Gymnema leaves, a colourless, crystalline substance having the empirical formula $C_6H_{14}O_6$ was isolated, which melted at 174° and had $[\alpha]_D -73{\cdot}9°$. When heated at 110°, it lost one molecular proportion of water; it formed a penta-acetyl derivative, $C_6H_7(O{\cdot}C_2H_3O)_5$, and a pentabenzoyl derivative, $C_6H_7(O{\cdot}C_7H_5O)_5$. From these facts it was seen that the above formula, $C_6H_{14}O_6$, could be appropriately modified to $C_6H_7(OH)_5,H_2O$, which represents the substance as a hydrated isomeride of quercitol.

The constitutional formula of quercitol, first proposed by Kanonnikoff, represents it as pentahydroxyhexahydrobenzene,



The correctness of this formula was proved by Kiliani and Schaefer (*Ber.*, 1896, 29, 1762), who obtained malonic acid on oxidation with potassium permanganate. Moreover, the same investigators have shown that *d*-quercitol, on oxidation with aqueous bromine, forms a diketone, $C_6H_8O_5$, which was isolated in the form of its dihydrazone, $C_{18}H_{20}O_3N_4$.

The substance isolated from the leaves of *Gymnema sylvestre*, when oxidised with potassium permanganate and sodium hypobromite respectively, showed a behaviour identical with that of *d*-quercitol. Like the latter, it afforded, on the one hand, malonic acid, and, on the other, a diketotrihydroxyhexahydrobenzene, which was isolated in the form of its dihydrazone (m. p. 209°).

It was thus demonstrated that our substance has the same constitution as *d*-quercitol, and can only differ from the latter stereo chemically; but, since *d*-quercitol has $[\alpha]_D$ +24·16°, the one cannot be the optical antipode of the other.

Pentahydroxyhexahydrobenzene has four asymmetric groupings, and eight optically active modifications are therefore possible, which may be represented as follows:

+ + + +	− + + +	+ + − +	+ + − −
− − − −	+ − − −	− − + −	− − + +

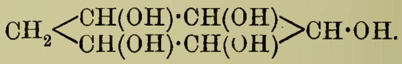
By uniting these four pairs, the corresponding racemic modifications would be obtained. The following two unresolvable inactive modifications are also possible:

+ − − + and + − + −.

Until a further number of these isomerides of quercitol are known, it will be impossible to assign a definite configuration either to *d*-quercitol or to the *l*-quercitol isolated from *Gymnema sylvestre*.

EXPERIMENTAL.

l-*Quercitol*,



$$\mathrm{CH_2}<\begin{matrix}\mathrm{CH(OH)\cdot CH(OH)}\\ \mathrm{CH(OH)\cdot CH(OH)}\end{matrix}>\mathrm{CH\cdot OH}.$$

The leaves of *Gymnema sylvestre* were extracted with hot alcohol and the liquid concentrated to a viscid syrup. Water was then added and the greater part of the remaining alcohol removed on the water-bath. After being allowed to cool, the precipitated resins were removed by filtration. Sulphuric acid was added to the clear filtrate until no further precipitate was produced, and this precipitate, which soon agglomerated to a resinous mass, was likewise removed by filtration. The free sulphuric acid was then removed by barium hydroxide, a slight excess of basic lead acetate subsequently added to remove the colouring matter, and the combined precipitates filtered off. After depriving the filtrate of lead by means of hydrogen sulphide, it was concentrated under reduced pressure to the consistency of a viscid syrup and then diluted with alcohol, when, after a few days, the *l*-quercitol separated in a nearly pure, crystalline form, which, after being filtered at the pump, thoroughly washed with alcohol, and recrystallised from dilute alcohol, was obtained in a perfectly pure state. The amount of this substance contained in the air-dried leaves is 0·6 per cent.

l-Quercitol melts at 174°. A determination of its specific rotatory power in aqueous solution gave the following result: $\alpha - 2°59'$; $l = 1$ dcm.; $c = 4·035$; $[\alpha]_D - 73·9°$.

It is readily soluble in water, very sparingly so in alcohol, and insoluble in all other ordinary solvents. It crystallises from water in colourless prisms containing one molecule of water, which is not lost on recrystallisation from absolute alcohol, but is eliminated when the substance is heated for some time at 100°. When crystallised from alcohol, it is obtained in the form of fine, colourless needles.

A portion of *l*-quercitol which had been recrystallised from alcohol was analysed :

0·1139 gave 0·1650 CO_2 and 0·0800 H_2O. $C = 39·5$; $H = 7·8$.
$C_6H_{12}O_5,H_2O$ requires $C = 39·5$; $H = 7·7$ per cent.

In another portion, which had been recrystallised from dilute alcohol, the water was determined by heating at 110°.

0·8963 lost 0·0881 H_2O. $H_2O = 9·8$.
$C_6H_{12}O_5,H_2O$ requires $H_2O = 9·9$ per cent.

This dried substance was then recrystallised from absolute alcohol, in which it was even more sparingly soluble than the hydrated substance, and analysed :

0·1009 gave 0·1600 CO_2 and 0·0674 H_2O. $C = 43·2$; $H = 7·4$.
$C_6H_{12}O_5$ requires $C = 43·9$; $H = 7·3$ per cent.

It was therefore practically anhydrous.

Penta-acetyl-l-*quercitol*, $C_6H_7(O{\cdot}C_2H_3O)_5$.

When *l*-quercitol is heated with acetic anhydride and sodium acetate, a vigorous reaction takes place before the boiling point of the anhydride is reached. After boiling for about one hour, the mixture was poured into water, when a heavy oil separated, which in a few minutes became solid. After recrystallisation from dilute alcohol, the substance was obtained in a pure state.

Penta-acetyl-*l*-quercitol crystallises in colourless needles, which melt at 124—125° when anhydrous, and at 87—97° when containing benzene of crystallisation. A determination of its specific rotatory power in chloroform solution gave the following result : $a = 0°42'$; $l = 1$ dcm. ; $c = 2·697$; $[a]_D - 26·0°$.

It is readily soluble in alcohol, ethyl acetate, acetone, benzene, ether, and chloroform, sparingly so in light petroleum, and insoluble in water. When crystallised from benzene, or a mixture of benzene and light petroleum, it contains one molecule of benzene, but from dilute alcohol it separates in an anhydrous state. The anhydrous acetyl derivative was analysed :

0·1320 gave 0·2467 CO_2 and 0·0706 H_2O. $C = 51·0$; $H = 5·9$.
0·1068 „ 0·2007 CO_2 „ 0·0576 H_2O. $C = 51·2$; $H = 5·9$.
$C_{16}H_{22}O_{10}$ requires $C = 51·3$; $H = 5·8$ per cent.

An attempt was made to determine the molecular weight of *l*-quercitol in phenol solution, but it was not sufficiently soluble. The acetyl derivative was therefore selected for this purpose, and its molecular weight was determined by the cryoscopic method in benzene solution.

0·4288 in 24·38 benzene gave $\Delta t - 0{\cdot}248^\circ$. M. W. = 348.
$C_{16}H_{22}O_{10}$ requires M. W. = 374.

The number of acetyl groups in this compound was determined by hydrolysing a weighed quantity of the substance with a known volume of standard alcoholic solution of sodium hydroxide and titrating the excess of alkali with standard acid. The percentage of acetyl found by this means was 80·3, the theoretical percentage for five acetyl groups being 78·9.

It was observed that the penta-acetyl-*l*-quercitol which had been crystallised from benzene melted at 87—97°, but after heating to 80° for a short time melted at 124—125°, which is the melting point of the anhydrous substance. The whole of the benzene was also given off in the course of two or three days at the ordinary temperature.

A portion of the acetyl derivative was crystallised from benzene, pressed on a porous tile until free from adhering solvent, and the amount of benzene of crystallisation determined by heating at 100° until the weight of the residue remained constant.

0·5200 lost 0·0880 C_6H_6. $C_6H_6 = 16{\cdot}9$.
0·7142 ,, 0·1239 C_6H_6. $C_6H_6 = 17{\cdot}3$.
$C_{16}H_{22}O_{10},C_6H_6$ requires $C_6H_6 = 17{\cdot}3$ per cent.

Pentabenzoyl-l-*quercitol*, $C_6H_7(O{\cdot}C_7H_5O)_5$.

The *l*-quercitol was benzoylated by the Schotten-Baumann method, and also by heating it with an excess of benzoyl chloride until hydrogen chloride ceased to be evolved; the products obtained were identical.

Pentabenzoyl-*l*-quercitol shows the same behaviour towards solvents as the acetyl derivative; it separates from alcohol in an amorphous state, melts at 133°, and is anhydrous. A determination of its specific rotatory power in chloroform solution gave the following result: $\alpha - 2^\circ 14'$; $l = 1$ dcm.; $c = 2{\cdot}826$; $[\alpha]_D\ -79{\cdot}0^\circ$.

On adding a quantity of light petroleum to a solution of the substance in a mixture of warm ethyl acetate and alcohol, needle-shaped crystals containing one molecule of alcohol slowly separated. These crystals, when dried in the air, melt at 116°, but the melting point is raised to

148° after drying at 100° for some hours. The amount of alcohol of crystallisation was estimated by heating at 120°.

0·7703 lost 0·0503 C_2H_6O. $C_2H_6O = 6·5$.
$C_{41}H_{32}O_{10},C_2H_6O$ requires $C_2H_6O = 6·3$ per cent.

The dried substance was then analysed :

0·1000 gave 0·2630 CO_2 and 0·0436 H_2O. C = 71·7 ; H = 4·8.
$C_{41}H_{32}O_{10}$ requires C = 71·9 ; H = 4·7 per cent.

l-Quercitol readily forms a phenylurethane, but this derivative crystallises with difficulty, and we were unable to obtain it in a pure state ; it melts indefinitely between 245° and 260°.

Oxidation with Sodium Hypobromite. Formation of a Diketotrihydroxyhexahydrobenzene, $C_6H_5O_2(OH)_3$.

By the oxidation of *d*-quercitol with bromine in the presence of water, Kiliani obtained a diketone which he isolated in the form of its dihydrazone, but did not obtain this in a state of purity (*Ber.*, 1896, **29**, 1762). In the case of *l*-quercitol, we have found that its oxidation can be effected much more quickly and more satisfactorily by the use of sodium hypobromite.

Twenty grams of *l*-quercitol and 90 grams of crystallised sodium carbonate were dissolved in water (about 400 c.c.) and the mixture cooled in ice. Thirty-five grams of bromine were then gradually added, and the mixture allowed to remain at the ordinary temperature for about 2 hours, when the colour of the bromine had disappeared. A slight excess of sulphuric acid was then added, and the liberated bromine removed by means of sulphur dioxide. The liquid, after being made slightly alkaline with potassium hydroxide, was acidified with acetic acid. Thirty grams of phenylhydrazine, dissolved in 30 grams of 50 per cent. acetic acid, were then added, and in the course of two days the mixture deposited a large quantity of dark red, tarry matter, mixed with minute needles of the dihydrazone. This sticky mass was collected at the pump, and the red, tarry matter removed by washing with ethyl acetate. A bright yellow, crystalline substance remained on the filter, which, after crystallisation from alcohol, in which it was somewhat sparingly soluble, melted with decomposition at 209°.

0·0963 gave 0·2233 CO_2 and 0·0519 H_2O. C = 63·2 ; H = 5·9.
0·1046 „ 0·2424 CO_2 „ 0·0566 H_2O. C = 63·2 ; H = 6·0.
0·1334 „ 19·8 c.c. moist nitrogen at 23° and 770 mm. N = 16·9.
$C_{18}H_{20}O_3N_4$ requires C = 63·5 ; H = 5·9 ; N = 16·5 per cent.

Oxidation with Potassium Permanganate. Formation of Malonic Acid.

A cold, dilute, aqueous potassium permanganate solution was gradually added to a cold, dilute, aqueous solution of *l*-quercitol. The colour of the permanganate was only very slowly discharged at first, but after a few portions had been introduced, the reaction proceeded much more quickly. When the equivalent of nearly eight atoms of oxygen had been added, the colour of the permanganate ceased to be discharged. The precipitated manganese dioxide was then removed and the oxalic and carbonic acids subsequently precipitated by the addition of an excess of calcium chloride. The filtrate was then evaporated to dryness, the powdered residue mixed with absolute alcohol, and the mixture boiled in a reflux apparatus for six hours, while dry hydrogen chloride was simultaneously passed through it. After distilling off the greater part of the alcohol, water was added, when the characteristic odour of ethyl malonate was perceptible. This liquid was then extracted with ether, and, after removing the latter, the residue was distilled, first under reduced, and finally under the ordinary pressure. A fraction boiling at 197—202° was analysed.

0·1175 gave 0·2256 CO_2 and 0·0804 H_2O. $C = 52·3$; $H = 7·6$.

$C_7H_{12}O_4$ requires $C = 52·5$; $H = 7·5$ per cent.

Kiliani (*loc. cit.*) identified the malonic acid formed by the oxidation of *d*-quercitol by analyses of its barium and calcium salts.

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